PATENT SPECIFICATION

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COMPLETE SPECIFICATION

NO DRAWINGS

Veterinary Compositions comprising 6α-methyl-17α-hydroxyprogesterone 17-acetate

We, THE UPJOHN COMPANY, a Corporation organized and existing under the laws of the State of Delaware, United States of America, of 301, Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to steroid compositions and more particularly to progestational compositions containing as the essential active ingredient 6alpha-methyl-17alpha-hydroxyprogesterone-17-acetate.

The steroid compound used in the compositions of the present invention is prepared according to the methods described in British Patent Specification No. 866,381.

In particular the present invention provides an oral pharmaceutical composition possessing progestational effects in ovulating mammals comprising 6alpha-methyl-17alpha-hydroxyprogesterone 17-acetate, a sedative and an oral pharmaceutical carrier. Such a composition may also comprise a diuretic. The dosage unit forms of such compositions comprise from 2 to 200 mgs of the active ingredient.

Also according to the invention there is provided an oral pharmaceutical composition with the above properties comprising 6alpha - methyl - 17alpha - hydroxyprogesterone 17-acetate an estrogenic substance as hereinafter defined and an oral pharmaceutical carrier. The estrogenic substance is preferably ethinyl estradiol or estradiol.

A sterile pharmaceutical composition according to the invention in dosage unit form comprises from about 15 to 35 mgs. of 6alpha - methyl - 17alpha - hydroxyprogesterone 17-acetate in 25 ccs. of a sterile fluid aqueous carrier.

A solid veterinary pre-mix possessing progestational effects in ovulating animals and birds according to the invention comprises 6alpha - methyl-17alpha-hydroxyprogesterone 17-acetate and an ingestible diluent. Such a composition may also contain an estrogenic substance as hereinafter defined. Preferably such compositions comprise from 0.1 to 5 percent by weight of 6alpha - methyl - 17alpha - hydroxyprogesterone 17-acetate.

An implanation pellet according to the invention possessing progestational effects in cattle comprises from about 1 to 300 mgs. of 6alpha - methyl - 17alpha - hydroxyprogesterone 17-acetate, from 10 to 30 mgs. of estradiol cyclopentylpropionate and a pelleting binder.

As used in the specification and claims of this application, oral pharmaceutical carrier is intended to include solid oral carriers as used in capsules, pills, pilules and tablets and liquid oral carriers as used in elixirs, solutions, suspensions and syrups. The term injectable pharmaceutical carrier is intended to include sterile aqueous solutions, sterile vegetable oils and sterile vegetable oil solutions. The term animal feed carrier is intended to include feed as used for live-stock, dogs, cats and the like. The term bird feed carrier is intended to include feed and mash as used for chickens, turkeys and the like.

It is especially advantageous to formulate the inventive composition in solid and liquid dosage unit forms for ease and economy of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages for animal, human and bird subjects, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specifications for the

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novel dosage unit forms of this invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved and (b) the limitations inherent in the art of compounding such an active material for therapeutic use in animal, human and bird subjects as disclosed in detail in this specification, these being features of the present invention. Examples of the dosage unit forms heretofore described are a tablet, a capsule, a pill, a powder packet, a wafer and a cachet; an ampule and a vial; and other forms alluded to herein. In accordance with the specific type of the final composition, the principal therapeutically active ingredient is formulated with the appropriate carrier. In the case of a solid dosage unit form, the said carriers comprise disintegrators, lubricants, diluents, binders and flavours. In the case of a liquid dosage unit form, the said carriers comprise water, edible oils, alcohol, glycols, colours, flavours, sweetening agents, suspending agents, surfactants and preservatives. In the case of an injectable dosage unit form, the carriers comprise water, ethanol, vegetable oils, preservatives, bactericidal and bacteriostatic agents, suspending agents, surfactants and isotonic agents. The animal and bird feed carriers comprise in balanced amounts the essential dietary constituents protein, fat, carbohydrate and minerals. Pre-mixes, for addition to animal and bird rations, contain ingestible bulking agents or diluents which can be dietary constituents, and 6?-methyl-17-hydroxyprogesterone 17-acetate in a concentration suited for the addition of the said ingredient in amounts calculated on the weight of the animal or bird under treatment.

Complementary therapeutically active ingredients which can be added to the compositions include estrogenic substances that is to say natural or synthetic substances which are capable of inducing estrus, for example, estrone, estradiol, estriol, ethinyl estradiol, estradiol cyclopentylpronionate or diethylstilbestrol, analgesics, for example, acetylsalicyclic acid, N-acetyl-*p*-aminophenol, salicylamide or phenacetin, sedatives, for example, phenobarbital, carbromal, reserpine or ectylurea, diuretics, for example, ethoxzolamide, hydrochlorothiazide or acetazolamide tranquilizers, for example, mepazine, perphenazine or oxanamide, muscle relaxants, for example, corisoprodol, chlorzoxazone or phenaglycodol.

The compositions of the invention are administered in varying dosages depending on the weight and condition of the mammals and birds under treatment, the route of administration, i.e., oral administration or parenteral injection, the particular affliction to be treated and the nature of the desired results.

The solid oral dosage unit forms comprise from about 2 to 200 mgs. of the essential active ingredient per dosage unit and are used from 1 to 4 times daily to provide total daily dosages of from about 2 mg. to 400 mgs. of the said ingredient. Adult human dosage would range from about 2 to 50 mgs. of the principal active ingredient per dosage unit.

The liquid oral dosage unit forms comprise from about 0.1 to 5% by weight of the principal active ingredient and are used from 1 to 4 times daily to provide total daily dosages of from about 2 to 200 mgs. of the said ingredient.

The dosage unit forms for injectable use include a single dose product comprising from about 15 to about 35 mgs. of 6alpha-methyl - 17alpha - hydroxyprogesterone 17-acetate in 25 ccs of a sterile fluid aqueous carrier. For convenience a product comprising from about 0.25 to about 10% by weight of the principal active ingredient may be made up and administered by parenteral injection in amounts of from about 0.1 to about 5 mls. to provide dosages of from about 0.25 to about 500 mgs. of the said ingredient.

The animal feed compositions comprise from about 0.0005 to 0.3% by weight of the principal active ingredient. The bird feed compositions comprise from about 0.0002 to 0.3% by weight of the principal active ingredient. The compositions provide the said ingredient in daily dosages to the variety of animals and birds of from about 0.1 to 15 mgs. per lb. of body weight.

The veterinary pre-mixes comprise from about 0.05 to 5% by weight of the principal ingredient. Said mixes are added to the daily rations in amounts calculated to provide the said ingredient in daily dosages of from about 0.1 to 15 mgs. per lb. of body weight.

The compositions of the present invention are novel and useful therapeutic preparations possessing unexpected, advantageous and beneficial results in the treatment of ovulating mammals and birds, for example, to re-establish normal endometrium-ovary-anterior pituitary relationships, in forestalling habitual and threatened abortion, in easing pre-menstrual tension in humans, and to prevent ovulation. In the practice of veterinary medicine, the compositions provide beneficial and advantageous results in the hormonal control of the reproductive cycle in animals, for example, by increasing in animals the number of implanted fertilized ova, of live births and the viability thereof; by synchronization of the estrual period in a group of swine, cattle, horses, sheep, dogs or cats; and by providing compositions and methods

to further weight gain with lessened estrogenic side effects in beef cattle. In birds there are provided compositions and methods to control the moulting period and the egg laying period of a flock, and to increase the number of eggs. The species variations in the estrual periods of the ovulating mammals must be taken into account in the several uses of the inventive compositions. When cycling, cows, horses, sheep, swine and cats have normal estrual periods about 21 days apart; dogs about 6 months apart. Thus, the treatment to synchronize the estrual period, whether oral or injectable, is continued for a maximum number of days ascertainable by reference to the last known estrual period of the particular species. Prolonged prevention of the estrual periods is brought about by continued treatment.

The following examples illustrate the best mode contemplated by the inventor of carrying out the invention and are not to be construed as limiting.

Example 1 Single dose injectable product

1000 mls. of a sterile solution are prepared from the following types and amounts of ingredients:

6α-Methyl-17α-hydroxy-progesterone 17-acetate	800 mgs.
Ethanol	760 mls.
Water for injection U.S.P. q.s. ad	1000 mls.

The steroid is dissolved in the ethanol and the solution made up to volume with the water. The whole is sterilized by passage through a sterilizing filter and filled aseptically into 25 mls. sterile ampoules. A 25-ml. daily dose containing 20 mgs. of the steroid is added to an intravenous infusion of saline with beneficial results in the treatment of endometriosis and abortion in humans.

200 mls. of polysorbate 80 U.S.P. is used in the above formula to provide another solution which is also useful in the treatment of endometriosis and abortion.

Example 2 Multiple dose injectable product

10,000 mls. of a sterile aqueous suspension are prepared from the following types and amounts of ingredients:

Each ml.		*Total*
5 mgs.	6α-Methyl-17α-hydroxy-progesterone 17-acetate	50 gms.
9 mgs.	Sodium chloride	90 gms.
0.2 mg.	Preservative	2 gms.
q.s.	Water for injection U.S.P. ad	10,000 mls.

The sodium chloride and preservative are dissolved in the water and the whole is sterilized by passage through a sterilizing filter. The steroid is micronized, sterilized by exposure to sterilizing vapor and added aseptically to the sterile aqueous solution. Dispersion is accomplished by mixing through a sterile homogenizer. The final suspension is filled aseptically into sterile vials. The duration of action of the suspension is prolonged. Beneficial results in the treatment of endometriosis and recurrent abortion in humans are obtained by the injection of 1 ml. one to three times monthly Inhibition of ovulation can be brought about by like dosages.

To provide a suspension for use to delay estrus in a group of cows the amount of the steroid acetate is increased to 1000 gms. providing a suspension containing 100 mgs. per ml. The injection of 1 ml. per cow per day for a maximum of 21 days is effective in delaying estrus. Upon cessation of treatment the group concurrently comes into estrus and can be bred successfully.

Similar suspensions containing 25 and 50 mgs. per milliliter, respectively, are prepared to obtain comparable results in the treatment of other species.

Example 3 Oral aqueous suspension

An aqueous suspension for oral administration, containing in each teaspoonful (approximately 5 mls.) 5 mgs. of 6α-methyl-17α-hydroxyprogesterone 17-acetate, is prepared from the following types and amounts of ingredients:

6α-Methyl-17α-hydroxy-progesterone 17-acetate	1 gm.
Preservative	2 gms.
Flavour	q.s.
Purified water U.S.P. q.s. ad	1000 mls.

0.2 gm. of estrogenic crystallizate (naturally occurring equine estrogens principally estrone, equilin and equilenin with a possible trace of estradiol) is added to the above formula.

The preservative and flavour are dissolved in the water. The finely powdered steroid is added and the whole homogenized.

A daily dose of 1 teaspoonful (5 mls.) gives beneficial results in the treatment of menstrual disorders in humans.

Example 4 Oral tablets

10,000 compressed tablets are prepared from the following types and amounts of ingredients:

Each tablet		*Total*
2.5 mgs.	6α-Methyl-17α-hydroxy-progesterone 17-acetate	25 gms.
300 mgs.	Ectylurea	3000 gms.
150 mgs.	Lactose	1500 gms.
3 mgs.	Acacia	30 gms.
65 mgs.	Starch, bolted	650 gms.
3 mgs.	Calcium stearate	30 gms.

The first four ingredients are finely powdered and mixed well. The whole is granulated with syrup-starch paste. The dried granules are well mixed with the starch-calcium stearate lubricant mixture. The whole is compressed into tablets.

Good results, with potentiated com-

plementary sedative action, are obtained in the treatment of threatened abortion at a dosage of 1 tablet per day.

350 gms. of ethoxzolamide is added to the above formulation to provide tablets useful for the treatment of pre-menstrual tension at a dosage of 1 tablet per day.

Example 5 Veterinary pre-mix

A dry pre-mix suited for incorporation into the normal diet of dogs is prepared from the following types and amounts of materials:

Part I

6α-Methyl-17α-hydroxy-progesterone 17-acetate	1 lb.
Liver protein	64 lbs.
Whole liver powder	60 lbs.
Fish meal	200 lbs.
Terra alba	24 lbs.
Dicalcium phosphate	100 lbs.
Ferrous gluconate powder	6 lbs. 8 oz.

Part II

Lecithin	32 lbs.
Wheat germ oil	11 lbs. 8 oz.
Brewer's yeast	200 lbs.

The Part I ingredients are mixed well together. The Part II wheat germ oil is mixed with the warmed lecithin and this mixture is added slowly to the brewer's yeast. The Part II mixture is then blended well with the Part I mixture to give the final product. Each 3.5 gms. (approximately 1 teaspoonful) of the final mixture contains 5 mgs. of the active ingredient, 6α-methyl-17α-hydroxyprogesterone 17-acetate. The proper amount of this pre-mix to be added to the animal ration can be calculated from the weight of the animal, the required dosage of active ingredient, and the amount of food consumed per day. In Kirk's Index of Treatment in Small-Animal Practice, published in 1951 by The Williams and Wilkins Company, there is a table on page 713 of food requirements in dogs:

TABLE IV

Food Maintenance Requirements of Mature Dogs

Body Weight (Kg.)	Grams of Food Per Animal Fresh Basis (70 Percent Moisture) Per Day
1	118
2	195
3	262
4	323
5	380
6	433
7	487
8	537
9	583
10	630
20	1040
30	1410
40	1740
50	2043

Another table, number V, is given on page 712 of the same publication:

TABLE V

The following table of approximate quantities of food per day, for maintenance of an adult animal in a well-nourished condition, is one which is considered fairly reliable as a general guide:

St. Bernards, Mastiffs, Great Danes	2.5-4.5 lbs.
Collies, Retrievers, Alsations and similar	1.5-2.5 lbs.
Greyhounds	1.8-2.5 lbs.
Airedales, Chows, Bulldogs and similar	.8-1.5 lbs.
Fox terriers, Welsh terriers, Scotties, etc.	8 -12 ozs.
Pugs, Poms, Pekingese	4 - 8 ozs.
Cats	4 - 8 ozs.

From the above tables the amount of premix to be added daily to the food can be calculated. For example, using Table I, to the 1740 gms. of food per day for the 40 kg. bitch, at a daily dosage of 0.5 mg. of active ingredient per kg. of body weight, 4 teaspoonfuls of food supplement are used. Using Table II, to the approximately 3 lbs. of food per day for the St. Bernard, at a total daily dosage of 10 mgs. of active ingredient, 2 teaspoonfuls of food supplement are added. The daily addition to the diet is continued as long as control of the estrual period is desired. Thereafter, the dog will come into heat and can be bred successfully.

Example 6 Animal feed composition

Ready-mixed feed is prepared in the following manner:

Commercial dog feed	100 lbs.
6α-Methyl-17α-hydroxy-progesterone 17-acetate	400 mgs.

The steroid is worked into a portion of the feed by careful mixing and the mix is incorporated uniformly into the remaining feed by milling. Each pound of the finished preparation contains 4 mgs. of the steroid providing a total daily dose of 5 mgs. for a 10 kilo dog eating 1 1/4 lb. of the feed per day. This daily dose is effective in preventing estrus in the female dog.

Example 7 Bird feed composition

A mash feed mix for hen chickens is prepared from the following types and amounts of materials:

Laying mash	100 lbs.
6α-Methyl-17α-hydroxy-progesterone 17-acetate	200 mgs.

The steroid is worked into a portion of the mash by careful mixing and the mix is incorporated uniformly into the remaining mash by milling. Each pound of the finished preparation contains 2 mgs. of the steroid providing a daily dose of 1 mg. of the progestational compound for a heavy breed hen eating 1/2 lb. of the mash per

day. This daily dose is effective in controlling the moulting period.

Example 8 Veterinary pre-mix with tranquilizer

Following the procedure of Example 9, a feed supplement containing perphenazine in addition to the steroid is prepared by adding 1 lb. of perphenazine to the Part I mixture, without impairing the effectiveness of the supplement in controlling the estrual period in bitches.

Example 9 Implantation pellet

1000 pellets for implantation in beef cattle are prepared from the following types and amounts of materials:

6α-Methyl-17α-hydroxyprogesterone 17-acetate	200 gms.
Estradiol cyclopentylpropionate	20 gms.

The two ingredients are blended with an inert diluent into a uniform mixture. The mixture is slugged and screened to a powdery consistency. The powder is compressed into pellets, each containing 200 mgs. of the progestational compound and 20 mgs. of the estrogenic compound.

Good results in the weight increase of growing beef cattle, especially in steers, are obtained by implantation of one pellet at the time the cattle go on full feed for fattening.

Example 10 Veterinary pre-mix

10,000 gms. of a pre-mix is prepared from the following types and amounts of ingredients:

6α-Methyl-17α-hydroxyprogesterone 17-acetate	300 gms.
Soybean meal	9700 gms.
Chloroform, U.S.P.	1500 mls.

A chloroform solution of the steroid active ingredient is prepared and incorporated gradually and uniformly into the soybean meal. After adequate mixing the whole is vacuum dried to remove any trace of chloroform.

Each gm. of the pre-mix contains 30 mgs. of the active ingredient. The pre-mix is added to the standard ration of a group of gilts to provide a daily dose to each gilt of 0.4 mg. of the steroid per lb. of gilt weight. Treatment for a maximum of 21 days prevents estrus. Thereafter the gilts come concurrently into estrus for breeding purposes. Like prevention of estrus in heifers occurs at a dosage of 0.4 mg. of the steroid acetate per lb. of heifer weight per day for a maximum of 21 days.

The addition to the rations of a group of bred sows of an amount of the pre-mix providing 1 mg. of the steroid acetate per lb. of sow body weight per day is beneficial in unexpectedly increasing the number of implanted fertilized ova. 150 mgs. of diethylstilbestrol can be added to the above formula to complement the action of the steroid acetate composition.

An equally satisfactory pre-mix is prepared by omitting the chloroform and using mineral oil to facilitate the preparation of a uniform pre-mix which is well suited for later incorporation into the animal ration.

Example 11 Veterinary bolus

9000 boluses, each containing 180 mgs. of the steroid acetate, are prepared from the following types and amounts of ingredients:

6α-Methyl-17α-hydroxyprogesterone 17-acetate	1620 gms.
Lactose	58,320 gms.

The above ingredients are blended and granulated with syrup-starch paste, and q.s. mineral oil is added. The granulation is then dried, lubricated with starch, talc and calcium stearate powders, and compressed with a 1 1/2" × 11/16" die.

The oral administration to a cycling mare of one bolus per day is effective in the control of estrus. The treatment is especially advantageous in racing mares.

Example 12 Oral tablets

Following the procedure of Example 4 5000 tablets are prepared from the following types and amounts of ingredients:

Each tablet		*Total*
5 mgs.	6α - Methyl - 17α - hydroxyprogesterone 17-acetate	25 gms.
0.01 mg.	Ethinyl estradiol	50 mgs.
150 mgs.	Lactose	750 mgs.
3 mgs.	Acacia	15 gms.
65 mgs.	Starch, bolted	325 gms.
3 mgs.	Calcium stearate	15 gms.

Good results in the inhibition of ovulation in humans are obtained at a daily dosage of 1 tablet orally.

Tablets equally suited for the inhibition of ovulation are prepared by using 250 and 1000 mgs., respectively, of the ethinyl estradiol in place of the 50 mgs. in the above formulation.

WHAT WE CLAIM IS:

1. An oral pharmaceutical composition possessing progestational effects in ovulating mammals comprising 6alpha-methyl-17alpha - hydroxyprogesterone-17-acetate, a sedative and an oral pharmaceutical carrier.

2. A composition as claimed in claim 1 in dosage unit form and comprising from about 2 to 200 mgs. of 6alpha-methyl-17alpha-hydroxyprogesterone-17-acetate.

3. A composition as claimed in claim 1 or 2 and comprising also a diuretic.

4. An oral pharmaceutical composition possessing progestational effects in ovulating mammals comprising 6alpha-methyl-17alpha-hydroxyprogesterone-17-acetate, an estrogenic substance as hereinbefore defined and an oral pharmaceutical carrier.

5. A composition as claimed in claim 4 and in unit dosage unit form which comprises from about 2 to 200 mgs. of 6alpha-methyl - 17alpha - hydroxyprogesterone-17-

acetate.

6. A composition as claimed in claim 4 or 5 in which the estrogenic substance is ethinyl estradiol or estradiol.

7. A sterile injectible pharmaceutical composition possessing progestational effects in ovulating mammals and in dosage unit form comprising from about 15 to 35 mgs. of 6alpha - methyl - 17alpha - hydroxyprogesterone-17-acetate in 25 ccs. of the sterile fluid aqueous carrier.

8. A solid animal feed mix possessing progestational effects in ovulating mammals comprising 6alpha-methyl-17alpha-hydroxyprogesterone-17-acetate and an animal feed carrier.

9. A composition as claimed in claim 8 and comprising from 0.0005 to 0.3 percent by weight of 6alpha - methyl - 17alpha-hydroxyprogesterone-17-acetate.

10. A solid bird feed mix possessing progestational effects in ovulating birds comprising 6alpha-methyl-17alpha-hydroxyprogesterone-17-acetate and a bird seed carrier.

11. A composition as claimed in claim 10 and comprising from 0.002 to 0.3 percent by weight of 6alpha-methyl-hydroxyprogesterone-17-acetate.

12. A solid veterinary pre-mix possessing progestational effects in ovulating animals and in birds comprising 6alpha-methyl - 17alpha - hydroxyprogesterone-17-acetate and an ingestable diluent.

13. A composition as claimed in claim 12 comprising from 0.1 to 5 percent by weight of 6alpha-methyl-17alpha-hydroxyprogesterone-17-acetate.

14. A composition as claimed in claim 12 or 13 and comprising also an estrogenic substance as hereinbefore defined.

15. An implantation pellet possessing progestational effects in cattle comprising from about 100 to 300 mgs. of 6alpha-methyl - 17alpha - hydroxyprogesterone-17-acetate, from about 10 to about 30 mgs. of estradiol cyclopentylpropionate and a pelleting binder.

16. A pharmaceutical composition comprising as its essential active ingredient 6alpha-methyl-17alpha-hydroxyprogesterone-17-acetate substantially as herein described with reference to any one of the Examples.

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